DATA EVALUATION RECORD - SUPPLEMENT

XDE-570 (FLORASULAM)

Study Type: OPPTS 870.3200 [§82-2]; Repeated-dose Dermal Toxicity Study in Rats

Work Assignment No. 4-01-128 E (MRID 46808225)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Bldg 100, Ste B.
Durham, NC 27713

Primary Reviewer
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 12/19/06

Secondary Reviewer
Stephanie E. Foster, M.S.

Signature: Stephanie E. Foster
Date: 12/19/06

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 12/19/06

Quality Assurance:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 12/20/06

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EPA Reviewer: Karlyn J. Bailey, M.S. **Signature:** [signature]
Registration Action Branch 2, Health Effects Division (7509P) **Date:** 5/31/07
EPA Secondary Reviewer: Myron Ottley, Ph.D. **Signature:** [signature]
Registration Action Branch 3, Health Effects Division (7509P) **Date:** 5/31/07
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: 28-Day Dermal Toxicity - Rats; OPPTS 870.3200 [§82-2] (rodent); OECD 410.

PC CODE: 129108 **DP BARCODE:** D331116
TXR#: 0054348

TEST MATERIAL (PURITY): XDE-570 (Florasulam; 99.3% a.i.; Lot # 940714)

SYNONYMS: XR-570, XRD-570, DE-570, N-(2,6-diflurophenyl)-8-fluoro-5-methoxy(1,2,4)triazolo(1,5-*c*)pyrimidine-2-sulfonamide

CITATION: Scortichini, B.H. and R.J. Kociba (1997) XDE-570: 28-Day repeated dose dermal toxicity study in Fischer 344 rats. The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID: 971042, July 15, 1997. MRID 46808225. Unpublished.

SPONSOR: Dow AgroSciences Canada, Inc., 2100- 450 1 St. SW, Calgary, AB, Canada

EXECUTIVE SUMMARY - In a repeated-dose dermal toxicity study (MRID 46808225), XDE-570 (Florasulam; 99.3% a.i.; Lot # 940714) in aqueous 0.5% Methocel was applied to the shaved skin of 5 Fischer 344 rats/sex/dose at dose levels of 0, 100, 500, or 1000 mg/kg/day, 6 hours/day for 7 days/week during a 28-day period.

No compound related effects in mortality, clinical signs, body weight, body weight gain, food consumption, hematology, clinical chemistry, urinalysis, organ weights, and gross or microscopic pathology parameters were observed in either sex.

At 1000 mg/kg/day, very slight (grade 1) edema and erythema at the treatment site were noted in 4/5 males beginning on Day 23. Dermal irritation was resolved by Day 28.

The systemic LOAEL is not determined and the systemic NOAEL is 1000 mg/kg/day.

The Dermal LOAEL is 1000 mg/kg/day, based on edema and erythema observed at the treatment site in males (4/5).

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.3200; OECD 410 for a 28-day dermal toxicity study in rats.

COMPLIANCE - Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided.

NOTE: This DER summarizes EPA conclusions regarding effects observed in the 28-day dermal toxicity study in rats. A detailed DER completed by the Canadian Pest Management Regulatory Agency (PMRA) is attached.

COMMENTS: EPA concurs with the PMRA toxicology evaluation, no conclusions have been changed.

46808225.PMRA.der
.pdf

Reviewer: Tom Morris , **Date:** April 12, 2000.

STUDY TYPE: Repeat-dose Dermal Toxicity - [rat] ; OPPTS 870.3200 (rodent); OECD 410.

TEST MATERIAL (PURITY): XDE-570 (Purity - 99.3%)

SYNONYMS: XR-570, XRD-570, DE-570, florasulam.

CITATION: Scortichini, B. H. and Kociba, R. J. July 15, 1997. **XDE-570: 28-Day Repeated Dose Dermal Toxicity Study in Fischer 344 Rats.** Performing Laboratory: The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, 48674. Laboratory Project Study ID: 971042. Unpublished

SPONSOR: Dow AgroSciences Canada Inc. (DAS).

EXECUTIVE SUMMARY: The repeat dose dermal toxicity of XDE-570 (Purity - 99.3%) was determined in male and female Fischer 344 rats. Five rats/sex/dose received dermal applications of the test substance as a suspension in aqueous 0.5% Methocel at dose levels of 0, 100, 500 or 1,000 mg/kg bw/d, 6 hours/day, 7 days/week for 28 days. The test substance was applied under occlusive wrapping to the shaved intact skin. The animals were sacrificed and necropsied on day 29.

There were no treatment-related effects on mortality, clinical signs, body weight, food consumption, haematology, clinical chemistry, organ weights or gross or systemic histologic pathology. At 1,000 mg/kg bw/d, 4/5 males exhibited very slight (grade 1) edema and erythema at the treatment site beginning on day 23. Dermal irritation was completely resolved by day 28.

The LOAEL was not determined. There were no treatment-related systemic findings in either sex at 1,000 mg/kg bw/d, the highest dose tested; therefore, the NOAEL for systemic toxicity was 1,000 mg/kg bw/d for both sexes.

This dermal toxicity study in the rat is acceptable / guideline and satisfies the guideline requirement for a repeat-dose dermal toxicity study (OPPTS 870.3200 rat) ; OECD 410 in rat.

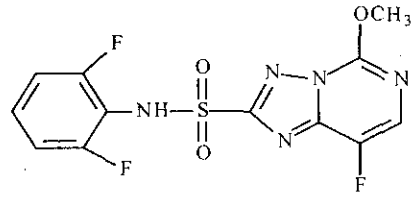
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** *XDE-570 as named in the study. Chemical Name (CA nomenclature):* N-(2,6-difluorophenyl)-8-fluoro-5-methoxy(1,2,4)triazolo(1,5-c)pyrimidine-2-sulphonamide

Description:	Fine, white powder
Lot/Batch #:	Lot # 940714 / Test Substance Number 100511
Purity:	99.3 % a.i. (determined by HPLC).
Compound Stability:	The test substance was determined to be stable in the vehicle for at least 15 days.
CAS #:	145701-23-1
Structure	



2. **Vehicle and/or positive control:** The test substance was administered as a suspension in aqueous 0.5% Methocel. The concentration of the test substance in the dosing suspensions was corrected to 100% based on the 99.3% purity value. Samples from the initial mix and all subsequent mixes were analysed to determine XDE-570 concentrations. Low- and high-dose suspensions were analysed for homogeneity by HPLC with UV detection and external standard quantification. Stability was not determined for dosing suspensions since previous data indicated that the test substance was stable in the vehicle for at least 15 days. The 100 and 1,000 mg/kg bw/d dosing suspensions were determined to be homogeneously mixed based on the relative standard deviations (RSD) of 0.86 and 1.67% for the 100 and 1,000 mg/kg bw/d dosing suspensions, respectively. The average dosages applied over the 28-day period of dosing for the 100, 500 and 1,000 mg/kg bw/d dose groups were 93, 98 and 95% of the targeted concentrations, respectively.

3. **Test animals:**

Species:	Male and female rats.		
Strain:	Fischer 344		
Age/weight at study initiation:	At study initiation, the rats were ≈8 to 9 weeks of age with a body weight range of 209.5 to 220.3 g for males and 128.9 to 141.7 g for females.		
Source:	Charles River Laboratories Inc., Raleigh, NC.		
Housing:	The animals were individually housed in stainless steel cages.		
Diet:	Certified Rodent Chow #5002 (Purina Mills Inc., St. Louis, MO) in meal form *ad libitum*		
Water:	Tap water *ad libitum*		
Environmental conditions:	**Temperature:**	Not provided.	It was indicated in the study report that the animals were housed in rooms designed to maintain adequate environmental conditions (temperature, humidity and photo-cycle).
	Humidity:	Not provided.	
	Air changes:	Not provided.	
	Photoperiod:	Not provided.	
Acclimation period:	At least 7 days.		

B. STUDY DESIGN:

1. In life dates - Start: February 13, 1997. End: March 12, 1997.

2. Animal assignment: Animals were randomly assigned to the test groups as summarized in Table 1 using a computer generated randomization program based upon body weight. The animals received topical applications for 6 hours/day, 7 days/week for 28 days. The animals were sacrificed and necropsied on study day 29 (March 13, 1997).

TABLE 1: Study design.

Test Group	Dose Level (mg/kg bw/d)	# Male	# Female
Control	0	5	5
Low	100	5	5
Mid	500	5	5
High	1,000	5	5

3. Dose selection rationale The highest dose level was based on the limit dose of 1,000 mg/kg bw/d (OPPTS 870.3200 (rodent), [§82-1]; OECD 410). The remaining dose levels were selected to provide dose-response data for any potential dermal irritation or systemic toxicity observed in the high-dose animals and to ensure definition of a no-observed-effect-level of the test substance.

4. Preparation and treatment of animal skin At least 24 hours prior to the first application, and as needed thereafter, the fur of each test animal was clipped from the dorsal area of the trunk over an area of at least 10% of the body surface. The test substance/vehicle suspension was evenly dispersed directly on the skin for approximately 6 hours/day. The exposure site was occluded with an absorbent gauze pad and non-absorbent cotton and the animal was wrapped with an elastic bandage to hold the test substance/vehicle suspension, gauze pad and cotton in place. Approximately 6 hours after application, the wraps, bandage, gauze and cotton were removed and the test site wiped with a water damped towel to remove any residual test substance. Animals in the control group were exposed to the vehicle suspension using the same procedure as described for the treated rats. The applied quantities of the test substance/vehicle suspension were calculated for each animal based on weekly body weights.

4. Statistics - All parameters examined statistically were initially tested for equality of variance using Bartlett's test. If the results of the Bartlett's test were significant, then the data for the parameter were subjected to a transformation to obtained equality of variance. The transformations examined were the common log, the inverse and the square root; these were applied in this order with a Bartlett's test following each transformation. When Bartlett's test was satisfied no further transformations were applied. If none of the transformations resulted in homogeneous variances, the transformation data or raw data with the lowest Bartlett's statistics were used. The selected data was then subjected to the appropriate parametric analysis. In-life body weight was evaluated using a three-way, repeat measure (RM) analysis of variance (ANOVA) for time (the repeated factor), sex and dose. In the three-way RM-ANOVA, the differences between the groups were detected primarily by the time-dose interaction. The first examination in the three-way RM-ANOVA was of the time-sex-dose interaction. If significant, the analysis was repeated separately for each sex without examining the results of other factors. The time-dose interaction was examined next. If the time-dose interaction was statistically identified, linear contrasts tested the time-dose interaction for the comparisons of each dose group to the controls. A Bonferroni correction was applied to the alpha level to compensate for the multiple comparisons with the control group. This correction controlled the experiment-wise error rate. This was applied only when comparisons were made to the control group and was applied for the time-dose interaction. Terminal body weight, organ weight (excluding testes), haematological parameters (excluding differential WBC), clinical chemistry parameters and urine specific gravity were evaluated using a 2-way ANOVA with the factors of sex and dose; differences between the groups were primarily detected by the dose factor. The first examination was whether the sex-dose interaction was significant; if it was, a 1-way ANOVA was done separately for each sex. Comparisons of individual dose groups to the controls were made with the Dunnett's test only when a statistically significant dose effect existed; this was subsequent to the evaluation of the sex-dose interaction. The form of the ANOVA, 1-way or 2-way, was determined by whether or not the analysis was

separated by sex or not. Results for testes weight were analysed using a 1-way ANOVA. If significant dose effects were determined in the 1-way ANOVA then separate doses were compared to controls using Dunnett's test. Food consumption was evaluated by Bartlett's test for equality of variances. Based on the outcome of Bartlett's test, a parametric or non-parametric ANOVA was performed. If significant, analysis by Dunnett's test or Wilcoxon Rank-Sum test with Bonferroni's correction, respectively, was performed. Statistical outliers were identified using a sequential method and were excluded from analysis. Because numerous measurements were statistically compared in the same group of animals, the overall false positive rate (Type I errors) could be much greater than the alpha levels might suggest. The final toxicological interpretation of the data considered other factors such as dose-response relationships and whether the findings are plausible in light of other biological and toxicological findings. Descriptive statistics only (means and standard deviations) were reported for food consumption. Means only were reported for urine specific gravity. Means and standard deviation tables were generated for all other variables.

C. METHODS:

1. Observations: Animals were observed once daily for clinical signs of toxicity, moribundity and mortality. Additionally, the animals were more thoroughly examined once weekly. Grading of the dermal application site for erythema, eschar formation and edema was conducted on all animals following removal of the wrap on the Friday of each week and on the day prior to necropsy and were evaluated using the Draize method. In addition, necrosis scabs and/or scars were noted if present; however, they were not graded.

2.Body weight Animals were weighed prior to initiation of the study and weekly during the treatment period.

3.Food consumption Food consumption data were collected from all rats approximately weekly. Food consumption was calculated as the difference between the initial weight of feed crock (g) and the final weight of the feed crock (g) divided by the number of days in the measurement cycle (d). Mean food consumption was reported as g food/animal/day. Food efficiency was not calculated.

4. Ophthalmoscopic examination: The eyes were examined prior to the start of the study using halogen illumination and at necropsy by an *in situ* technique by application of moistened microscope slide to each cornea while utilizing fluorescent illumination.

5. Haematology & Clinical Chemistry: Following an overnight fast, the animals were anaesthetised with methoxyflurane and blood samples were collected from all animals immediately prior to necropsy via puncture of the orbital sinus. Samples for haematology were mixed with ethylenediaminetetraacetic acid (EDTA) and blood smears were prepared and stained with Wright's stain. Clinical chemistry samples were collected and serum separated from cells as soon as possible following blood collection. The haematological and clinical chemistry parameters marked with an (X) in tables (a) and (b), respectively, were examined.

a. Haematology

X	Haematocrit (HCT)*	X	Leukocyte differential count*
X	Haemoglobin (HB)*		Mean corpuscular haemoglobin (MCH)
X	Leukocyte count (WBC)*		Mean corpuscular haemoglobin concentration (MCHC)
X	Erythrocyte count (RBC)*		Mean corpuscular volume (MCV)

X	Platelet count* (PLT)		Reticulocyte count
	Blood clotting measurements*	X	RBC morphology
	(Partial Thromboplastin time)	X	WBC Morphology
	(Thrombin Clotting time)	X	Platelet morphology
	(Prothrombin time)		

* Recommended for dermal toxicity studies based on Guideline 870.3200.

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium* (CA)	X	Albumin* (ALB)
X	Chloride* (Cl)	X	Blood creatinine* (CREA)
	Magnesium	X	Blood urea nitrogen* (UREA)
X	Phosphorus* (P)	X	Total Cholesterol (CHOL)
X	Potassium* (K)	X	Globulins (GLOB)
X	Sodium* (NA)	X	Glucose* (GLUC)
	ENZYMES	X	Total bilirubin (TBILI)
X	Alkaline phosphatase (AP)	X	Total serum protein (PROT)*
	Cholinesterase (ChE)	X	Triglycerides (TRIGL)
X	Creatine phosphokinase (CPK)		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine amino-transferase (also SGPT)* (ALAT)		
X	Serum aspartate amino-transferase (also SGOT)* (ASAT)		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase (GDH)		

* Recommended for dermal toxicity studies based on Guideline 870.3200.

6. Urinalysis * Urine samples were collected by manual compression of the bladder from all non-fasted animals during the week prior to necropsy. If an insufficient quantity was collected from a particular animal, a second attempt was made as soon as possible. The urinalysis parameters marked with an (X) in the following table were examined.

X	Appearance	X	Glucose (GLUC)
	Volume	X	Ketones (KETO)
X	Specific gravity (SpGr)	X	Bilirubin (BILI)
X	pH *	X	Blood *
X	Sediment (microscopic)		Nitrate
X	Protein (PROT)	X	Urobilinogen (UROBIL)
X	Colour		

* Optional for dermal toxicity studies.

7. Sacrifice and Pathology Terminal fasted body weights were recorded for all animals. At the time of necropsy, animals were anaesthetised by inhalation of methoxyflurane vapours, blood/serum samples obtained from the orbital sinus, their tracheas exposed and clamped and the animals euthanised by decapitation. A complete gross necropsy was conducted on all animals. The necropsy included *in situ* examination of the eye by a glass slide technique utilizing fluorescent illumination. The nasal cavity was flushed with neutral, phosphate-buffered 10% formalin. The lungs were inflated to an approximately normal inspiratory volume with neutral, phosphate-buffered 10% formalin. The organs/tissues, in whole or in part, marked with an (X) in the following table were fixed in 10% buffered formalin. Organs/tissues marked with a (XX) in the following table were weighed prior to fixation. Samples of skin were obtained from the clipped test substance application site, an unclipped site adjacent and caudal to the application site and from the inguinal region for collection of skin and mammary tissue. All preserved tissues from all animals in the control and high-dose groups were processed by standard procedures. Paraffin embedded tissues were sectioned at approximately 6 µm, stained with hematoxylin and eosin and examined by light microscopy. In addition all gross lesions plus skin from the site of application and skin adjacent to the site of application from all animals in the low- and intermediate-dose groups were also processed for subsequent histopathologic examination.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	*Bone marrow**	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	X	Thymus*+		*GLANDULAR*
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Mammary gland*
X	Rectum*	X	Urinary bladder*	X	Parathyroid*
XX	*Liver**+	XX	*Testes**+	X	Thyroid*
	Gall bladder*	X	Epididymides*+		OTHER
X	Pancreas*	X	Prostate*	X	Bone
	RESPIRATORY	X	Seminal vesicles*	X	*Skeletal muscle*
X	Trachea*	X	Ovaries*+	X	Skin* (treated & untreated areas)
X	Lung*	X	Uterus*+	X	All gross lesions and masses*
X	Nose*	X	Vagina		
X	Pharynx*	X	Cervix		
X	Larynx*				

* Recommended for dermal toxicity studies based on Guideline 870.3200
\+ Organ weights required.
X Organ fixed.
XX Organ weighed prior to fixation.

II. RESULTS

A. Observations :

1. Mortality - There were no mortalities.

2. Clinical signs of toxicity - There were no treatment-related clinical observations.

3. *Dermal Irritation* - At 1,000 mg/kg bw/d, 4/5 males exhibited very slight (grade 1) edema and erythema at the treatment site beginning on day 23. These dermal irritation findings were completely resolved by day 28. No signs of dermal irritation attributed to treatment were observed in either sex at 100 or 500 mg/kg bw/d or in females at 1,000 mg/kg bw/d at any time during the study.

B. Body weight and weight gain: Body weight and body-weight gain were unaffected by treatment at dose levels up to and including 1,000 mg/kg bw/d in both sexes.

C. Food consumption:

1. Food consumption - Food consumption was unaffected by treatment at dose levels up to and including 1,000 mg/kg bw/d in both sexes.

2. Food efficiency Not provided in study report. However, body weight, body-weight gain and food consumption were unaffected by treatment at dose levels up to and including 1,000 mg/kg bw/d in both sexes.

D. Ophthalmoscopic examination - There were no treatment-related ophthalmoscopic findings in either sex up to and including 1,000 mg/kg bw/d.

E. Blood analyses

1. Haematology - There were no treatment-related changes in haematological parameters in either sex up to and including 1,000 mg/kg bw/d. Some haematological parameters reached statistical significance, primarily at the low dose (Table 2). In the absence of any dose-response pattern or histopathological correlate they were considered representative of normal biological variation and unrelated to treatment.

TABLE 2. Haematological findings. (a)

Dose Level (mg/kg bw/d)	0	100	500	1,000
Males (5 animals/dose)				
WBC (x 10^3/mm^3)	6.67 ± 0.58	8.83 ± 0.98 *	8.19 ± 0.84	8.26 ± 0.84
Females (5 animals/dose)				
WBC (x 10^3/mm^3)	6.36 ± 0.59	6.65 ± 0.70 *	6.73 ± 0.85	6.46 ± 1.53
RBC (x 10^6/mm^3)	8.19 ± 0.19	7.56 ± 0.42 *	8.22 ± 0.23	7.90 ± 0.32
HGB (g/dL)	15.1 ± 0.2	14.5 ± 0.2 *	15.1 ± 0.2	14.4 ± 0.4 *
HCT (%)	43.0 ± 1.0	39.8 ± 1.7 *	43.1 ± 1.1	41.7 ± 1.3

(a) Data obtained from pages 45 to 50 of the study report.
* Statistically different from control mean by Dunnett's test, $p \leq 0.05$.

2. Clinical Chemistry - There were no treatment-related changes in clinical chemistry parameters in either sex up to and including 1,000 mg/kg bw/d.

F. Urinalysis - There were no treatment-related changes in urinalysis parameters in either sex up to and including 1,000 mg/kg bw/d.

G. Sacrifice and Pathology:

1. Organ weight - There were no biologically or toxicologically relevant treatment-related changes in organ weights in either sex up to and including 1,000 mg/kg bw/d. Relative adrenal weights were statistically significantly increased in both sexes at 1,000 mg/kg bw/d (Table 3). However, in the absence of any significant change in absolute adrenal weights in either sex at this dose level and in the absence of any corroborating laboratory, gross pathological or histopathological findings, this was not considered to be biologically or toxicologically relevant and was most likely an incidental finding.

TABLE 3. Absolute (g ± SD) and relative (g/100 g bw ± SD) organ weights. (a)

Dose Level (mg/kg bw/d)		0	100	500	1,000
Males (5 animals/dose)					
Adrenals	Absolute	0.050 ± 0.002	0.046 ± 0.003	0.051 ± 0.006	0.051 ± 0.007
	relative	0.0234 ± 0.009	0.0221 ± 0.0015	0.0241 ± 0.0024	0.0249 ± 0.0036 *
Females (5 animals/dose)					
Adrenals	Absolute	0.048 ± 0.004	0.047 ± 0.004	0.049 ± 0.004	0.055 ± 0.003
	Relative	0.0373 ± 0.0035	0.0363 ± 0.0028	0.0389 ± 0.0032	0.0423 ± 0.0042 *

(a) Data obtained from pages 59 to 60 of the study report.
* Statistically different from control mean by Dunnett's test, $p \leq 0.05$.

2. Gross pathology - There were no treatment-related gross pathological findings in either sex up to and including 1,000 mg/kg bw/d.

3. Microscopic pathology - There were no treatment-related histopathological findings up to and including 1,000 mg/kg bw/d.

III. DISCUSSION

A. Investigators' conclusions (extracted from page 27 of the study report): "Repeated dermal application of XDE-570 resulted in no treatment-related systemic effects in male or female rats or dermal irritation in female rats at any dose level tested. Very slight transient dermal irritation at the application site was observed only in male rats receiving applications of 1000 mg/kg/day. No signs of dermal irritation were observed in male rats at 100 or 500 mg/kg/day. Therefore, under the conditions of this study, the no observed effect level (NOEL) was the limit dose of 1000 mg XDE-570/kg/day for male and female Fischer 344 rats. The NOEL for dermal test site irritancy was 500 mg/kg/day in males and 1000 mg/kg/day in females."

B. Reviewer comments: There were no treatment-related effects on mortality, clinical signs, body weight, food consumption, haematology, clinical chemistry, organ weights or gross or systemic histologic pathology. At 1,000 mg/kg bw/d, 4/5 males exhibited very slight (grade 1) edema and erythema at the treatment site beginning on day 23. Dermal irritation was completely resolved by day 28.

The LOAEL was not determined. There were no treatment-related systemic findings in either sex at 1,000 mg/kg bw/d, the highest dose tested; therefore, the NOAEL for systemic toxicity was 1,000 mg/kg bw/d for both sexes.

C. Study deficiencies: This study was submitted under DACO 4.8 (Other Studies/Data/Reports), it should have been submitted under DACO 4.3.5 (Short-term dermal - 21/30 day). Room temperature and humidity as well as the number of air-changes and photo-period were not provided in the study report, however, it was indicated in the study report that the animals were housed in rooms designed to maintain adequate environmental conditions. Due to the method of urine collection (manual compression of the bladder) urine volume was not determined. However, according to OECD Guideline 410 (Repeated Dose Dermal Toxicity: 21/28-day Study) urinalysis is not required on a routine basis, but only when there is an indication based on observed or expected toxicity. No treatment-related urinalysis findings were observed; therefore, this should not affect the outcome of the study. There are no deficiencies which would impact on the outcome of the study; therefore, this study is acceptable and satisfies the guideline requirement for a repeat-dose dermal toxicity study (OPPTS 870.3200 rat) ; OECD 410 in rat.